Remarks:

For convenience, Pages 2 and following of the official action are presented below in italics with corresponding responses interspersed between paragraphs:

Application/Control Number: 09/841,763 Art Unit: 1634 [Page 2]

DETAILED ACTION

Continued Examination Under 37 CFR 1.114 1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 27, 2003 has been entered.

The Examiner is thanked for withdrawing the Final Rejection, entering new Claims 39-58, and continuing the prosecution of the Application.

Claim Rejections - 35 USC § 112

2. Claims 44, 48, 51, 54 are rejected under 35 U.S.C.112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the phrase "less than about 0.1 units" in claim 44. The phrase "less than" typically indicates a maximum point. The phrase "less than" however, is contravened by the term "about" which implies that values above and below 0.1 units of endotoxin are permitted. Further, the extent of variance permitted by "about" is unclear in this context. In Amnen, Inc. v. Chunai Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase[Page 3]

"at least about" indefinite where the metes and bounds of the term were not defined in the specification. Similarly, "less than about" is also indefinite.

The phrase "at least about" has been cancelled from Claim 44. This is merely a change in expression, as those skilled in the art will know that limits of this sort must be read in view of different methods of determination, test tolerances and other factors.

Regarding claims 48, 51 and 54, the phrase "(i.e. hexamine ... chromium (111))" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The objected-to phrase has been cancelled. The phrase remains in other subclaims without the "i.e.".

> *Claim Rejections - 35 USC § 102 &103. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:*
> *A person shall be entitled to a patent unless*
> *(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*
> *4. Claims 39-41, 43-46 and 56-58 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al (Biotechniques (1996) 21(1):92-99).*
> *Davis teaches double CsCl banded DNA, specifically of vectors with luciferase or HBV envelope genes (see page 94, column 1).*
> *Davis demonstrates that the DNA contains less than 3% RNA by weight (see figure 4, where the HPLC standard shows no RNA is present as well as page 97, column 1, where Davis states that no RNA was detected.*
> *With regard to claims 40, 43, it is an inherent property of the double CsCl banded DNA that there is less than 0.0001 percent RNAse by weight since the proteins are separated from the closed circular DNA in the centrifuge tube and the combination of alkaline lysis and two CsCl banding separations inherently achieve complete removal of [Page 4] RNAse. Further, Davis notes that the preparation was free of protein contamination (see page 97, column 1).*
> *With regard to claim 41, Davis teaches expression of HBV proteins for genetic immunization (see page 96, column 1).*
> *With regard to claims 44-46, Davis expressly teaches that there is less than 0.012 EU/ug DNA (see page 97, column 2).*
> *With regard to claims 56-58, Davis teaches purified double CsCl banded DNAwhich is inherently free of animal derived proteins and ribonucleases as discussed above. Further, Davis notes that the preparation was free of protein contamination (see page 97, column 1).*

While a plasmid DNA prepared by Davis' 2X CsCl bouyant density gradient centrifugation might approach the compositions recited in some claims, Claim 39 has now been amended by adding the wording of subclaims 44 and 48 and reciting the additional composition of the preferred stripping solutions. The composition of amended Claim 39 results from the compaction process taught in the present application. Incidental similarities in the Davis reference are readily distinguished because Davis uses a different process for different purposes and does not purify as does the present invention, therefor Davis does not form the compositions of Claim 39 or Claim 62.

5. Claims 39-46 and 56-58 are rejected under 35 U.S.C.102(b) as being anticipated by Webster et al (Vaccine (1994) 12(8)1495-1498) as evidenced by Davis et al (Biotechniques (1996) 21 (1):92-99).

Webster teaches double CsCl banded DNA, specifically of vectors with influenza proteins for use as a vaccine (see page 1495, column 2, subheading "DNA vaccines").

With regard to claims 40, 43-46 and 56-58, Davis evidences that CsCl double banded DNA is free of RNAse, protein contamination and endotoxin as discussed above. Therefore, the double CsCl banded DNA of Webster inherently meets the requirements of claims 40, 43-46 and 56-58. 6. Claims 39, 40 and 43-58 are rejected under 35 U.S.C.102(b) as being anticipated by Moradpour et al (Biochem. Biophys. Res. Comm. (1996) 221 :82-88) as evidenced by Davis et al (Biotechniques (1996) 21 (1):92-99). [Page 5]

While a plasmid DNA prepared by Webster's 2X CsCl bouyant density gradient centrifugation might aprocah the compositions recited in some claims, Claim 39 has now been amended by adding the wording of subclaims 44 and 48 and reciting the additional composition of the preferred stripping solutions. The composition of amended Claim 39 results from the compaction process taught in the present application. Incidental compositional similarities in the Webster reference are readily distinguished because Webster uses a different process for different purposes and does not purify as does the present invention, therefor Webster does not form the compositions of the independent Claim 39 or 62.

Moradpour teaches a composition which comprises double CsCl banded DNA (see page 83, subheading "plasmid constructs") which is mixed with cholesterylspermidine (see page 83, subheading "transfection experiments").

The Moradpour reference, does not teach the current invention. Moradpour, et. al. take a cholesterol deriviative and covalently attach it to spermidine. Then they take 2X CSCl purified plasmid (as detailed in the Sambrook reference initially cited in the present application (and which is referenced in Moradpour's paper) and mix it with the cholloesteryl-spermidine to form cationic liposomes. Cationic liposomes, including lipids linked to polyamines, have long been known for years. Basically there the cations (spermidine in Moradpour's case) attached to the DNA while the cholesterol molecules form an outer skin around the inner DNA layer. These "liposomes" are used to increase

the rate of transfection of cells with DNA. So Moradpour uses cholestyryl-spermidine only to get DNA into his cells as a therapeutic or vaccine. This has no impact on purity and is not used as a purification step. Polyamines are known to bind DNA, but before the present application, polyamines were not used to selectively *purify* DNA.

Claim 39 has now been amended by adding the wording of subclaims 44 and 48 and reciting the additional composition of the preferred stripping solutions. The composition of amended Claim 39 results from the compaction process taught in the present application. Incidental similarities in the Mouradpour reference are readily distinguished because Mouradpour uses a different process for different purposes and does not purify as does the present invention, therefor Moradpour does not form the compositions of Claim 39 or Claim 62.

Neither Davis, nor Webster, nor Mouradpour teach the claimed low-RNA, Low-EU compositions with stripping solution which result from the new method of Applicants' issued parent patent and thus contain their Applicants' preferred compaction agents and stripping agents.

> *With regard to claims 40, 43-46 and 56-58, Davis evidences that CsCl double banded DNA is free of RNAse, protein contamination and endotoxin as discussed above. Therefore, the double CsCl banded DNA of Moradpour inherently meets the requirements of claims 40, 43-46 and 56-58.*
> *With regard to claims 47-55, Moradpour expressly teaches a composition in which the double CsCl banded DNA is mixed with spermidine, which is a polyamine that is expressly listed in the claims (see page 83, subheading "transfection experiments").*

The Davis reference, also does not teach the current invention. Incidental similarities in the Davis reference are readily distinguished because Davis uses a different process for different purposes and does not purify as does the present invention, therefor Davis does not form the compositions of independent Claims 39 and 62. Even if plasmid DNA

prepared by 2X CsCl bouyant density gradient centrifugation might approach the compositions recited in some of the present claims, Davis' compositions would not include the stripping agent recited in the claims. Butyl Cationic Liposomal delivery technologies are not purification-related as discussed above, thus Davis is using a different method for a different purpose and does not produce the presently claimed compositions.

Claims 44, 48, 50, 53 and 58 have been cancelled so that their wording may be included in other claims.

New Claim 62 recites the ionic strength based on page 26, line 13 of the application.

New Claim 63 is supported at page 23 line 6-29 and recites the chelating agent that binds free metals and compaction agents in solution:

"... Alternates include EGTA,EDTA (ETHYLENEDIAMINETETRAACETIC ACID): other preferred chelating agents include:

Nitrilotriacetic acid, NTA: N(CH2COOH)3
Hydroxyethylethylenediaminetriacetic acid, HEDTA:=20
(HOOCH2C)2NCH2CH2N(CH2COOH)(CH2CH2OH)
Diethylenetriaminepentaacetic acid, DTPA:=20
(HOOCH2C)2NCH2CH2N(NCH2COOH)CH2CH2N(CH2COOH)2
1,2-Diaminopropanetetraacetic acid, 1,2-PDTA
(HOOCH2C)2NCH(CH3)CH2N(CH2COOH)2
1,3-Diaminopropanetetraacetic acid, 1,3-PDTA:
(HOOCH2C)2NCH2CH2CH2N(CH2COOH)2
2,2=B4-Ethylenedioxybis[ethyliminodi(acetic acid)], EGTA:=20
(HOOCH2C)2NCH2CH2OCH2CH2OCH2CH2N(CH2COOH)2
Bis(carboxymethyl)diaza-18-crown-6,
(HOOCH2C)N(CH2CH2OCH2CH2OCH2CH2)2N(CH2COOH)
1,10-bis(2-pyridylmetyl)-1,4,7,10-tetraazadecane, BPTETA:=20
(C6H4N)CH2NHCH2CH2NHCH2CH2NHCH2CH2NHCH2(C6H4N)."

Conclusion

7. The prior art made of record and not relied upon is considered pertinent to

applicant's disclosure. Butash et al (Biotechniques (2000) 29(3):610-619) also notes that CsCl banded DNA has less than 0.001 EU/ug DNA).

References cited which are not relied on for rejections, will not be commented on except to state the none of them, either alone or in combination with other references would anticipate the invention under 35 USC 102 or render it obvious under 35 USC 103..

Conclusion: Neither Davis, nor Mouradpour nor Webster teach the claimed low-RNA, Low-EU compositions which result from the new method of Applicants' issued patent and thus contain their preferred compaction agents.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-3086568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. [Page 6]

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone namer is 703-308 0196. – Jeffrey Fredman, Primary Examiner, Art Unit 1634

The claims have been clarified and broadened merely by addition of wording from the original specification; no new matter has been added and no estoppel is involved. The changes were not required by the art cited because the original claims themselves distinguished from the references relied on.

The fee (small entity) for the one-month extension and any other necessary (small entity) charges can be charged to USPTO Deposit Account 20-336 of Technology Licensing Co. LLC. Correspondence may be addressed to Customer No. 26830.

The Examiner is especially invited to telephone Applicants' Attorney if that would expedite prosecution and disposal of this Application.

Respectfully submitted,

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